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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,080	09/24/2008	Mervi Ahlroth	GJE.7664	9433

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
03/18/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slepatents.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,080	AHLROTH ET AL.	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of July 1, 2010 on October 1, 2010 and January 10, 2011.

No amendment to the claims was made. Claims 1-5, 8-14 are withdrawn.

Claims 6, 7, 15-18, drawn to a fusion protein comprising an endonuclease fused to an integrase, are under consideration.

Withdrawn Objection

Specification

Applicant's arguments, see Applicant's response, filed January 10, 2011, with respect to sequence compliance have been fully considered and are persuasive. Applicant has amended the specification to add SEQ ID NOs. and has submitted a new sequence listing and sequences in computer readable format (CFR). The objection of the sequence compliance has been withdrawn.

Maintained Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6, 7, 15-18 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bushman, WO 95/32225, published November 30, 1995, see IDS, Mannino et al., 1999, Biochemistry, 38: 16189-16186, see IDS, Dujon et al., US Patent 5,474,896, patented December 12, 1995, for reasons of record, July 1, 2010.

The rejection of July 1, 2010 is copied below for Applicant's convenience.

Bushman teaches that retroviral vectors are a popular means for delivering DNA in gene therapy protocols. However, insertion of retroviral DNA can result in inactivation or ectopic activation of cellular gene, thereby causing diseases. Thus, methods for site-specifically controlling the location of integration of retroviral vectors are desired to overcome this problem (Bushman, page 2, 5th parag. to page 3, 2nd parag.). Bushman teaches that the chimeric protein comprises a “first domain” that attaches the chimeric protein to target nucleic acid and a “second domain" that integrates donor nucleic acid into the target nucleic acid. The first domain can be either a “DNA-binding domain” or a “protein-binding domain” that is operative to couple and/or associate the chimeric protein with a recognition sequence on the target nucleic acid. DNA-binding domains are typically derived from DNA binding proteins and are found in proteins including transcription control proteins, recombination enzymes, and DNA-modifying enzymes. DNA-modifying enzymes include restriction enzymes, DNA-repair enzymes, site-specific methylases, and the like. The second domain functions to promote integration of donor nucleic acid into target nucleic acid. Typically, the second domain is derived from an integrase protein. One preferred integrase protein is a retroviral integrase, which includes HIV-1 (Bushman, pages 6-12; more specifically, see page 6, parag. 1-3 under Detailed Description of the Invention, page 9, 3rd parag., page 10, 3rd parag. to page 11).

While Bushman teaches making chimeric proteins comprising a DNA binding domain and an integrase, wherein the DNA binding domain can be obtained from a restriction enzyme and wherein the integrase can be obtained from a retrovirus, including that of HIV-1, Bushman does not teach using restriction enzymes PpoI, CreI, and H98A.

At the time of filing, Mannino et al. teach that homing endonucleases, like type II bacterial restriction endonucleases, catalyze the hydrolytic cleavage of DNA in a site-specific manner. However, the recognition sequences of homing endonucleases are, in general, substantially longer than are those of restriction endonuceases. Recognition sequence of

homing endonucleases range from 15 to 40 base pairs and these enzymes show degeneracy in the recognition of these target sites that resembles the degeneracy of transcription factors (Mannino et al., page 16178, 1st col., 1st parag.). PpoI and its mutant, H98A, are two examples of homing endonucleases (Mannino et al., page 16179, 1st col. under Production of I-PpoI Endonuclease in Escherichia coli). It is noted that an artisan would have used a homing endonuclease because longer recognition sites in the genome are rarer than recognition sites that restriction endonucleases bind. This means that a smaller number of sites are recognized in the genome by homing endonucleases than restriction endonucleases and would also mean that fewer sites in the genome are cut by the homing endonuclease fused to an integrase. This would address Bushman's issue that one problem with integrases is that it inserts in the genome, sometimes hitting critical genes. Using an endonuclease that has a small number of potential sites to integrate would reduce the probability that the endonuclease-integrase fusion protein of hitting a critical gene.

With regard to using CreI (claim 16), the art teaches that CreI is also a homing endonuclease (Dujon et al., col. 10, first table) and an artisan would have used CreI because it is a functional equivalent with regard to being an endonuclease that recognizes a long nucleotide sequence.

With regard to the claims being drawn to the endonuclease being specific to a site in an abundant rDNA locus (claim 6), it is noted that this is an inherent property of homing endonucleases. For example, Makino et al. teach that PpoI cleaves recipient rDNA at the site of intron integration (Makino et al., page 16178, 1st col., 2nd parag. to 2nd col.).

Applicant's arguments filed October 1, 2010 have been fully considered but they are not persuasive.

Applicant indicates that the cited references, taken alone or in combination, do not teach or suggest the claimed invention. The primary reference cited under the rejection, Bushman, discloses the integration of viruses containing the integrase-LexA fusion protein. There is no natural genomic target for an intergrase-LexA fusion protein. The binding sites are not unique in the human genome, meaning that LexA is not feasible for safe transgene integration. The present invention is direct to solving a

completely different problem, i.e., the specific integration of a transgene comprising retrovirus-like nucleic acid into a eukaryotic genome (Applicant's emphasis, Applicant's response, pages 8-9). In response, this is not persuasive. The instant rejection is a 103 and not a 102. Bushman is not limited to teaching an integrase-LexA fusion protein. Bushman teaches that while retroviral vectors are a popular means for delivering DNA in gene therapy protocols, insertion of retroviral DNA can result in inactivation or ectopic activation of cellular genes, thereby causing diseases. Thus, methods for site-specifically controlling the location of integration of retroviral vectors is desired (Bushman, page 2, 5th parag. to page 3, 2nd parag.). Bushman also teaches that to address this problem, a chimeric protein, comprising a "first domain" that attaches the chimeric protein to a target nucleic acid and a "second domain" that integrates donor nucleic acid into the target nucleic acid. The first domain can either be a "DNA-binding domain" or a "protein-binding domain" that is operative to couple and/or associate the chimeric protein with a recognition sequence on the target nucleic acid. DNA-binding domains are typically derived from DNA binding proteins, including restriction enzymes. The second domain functions to promote integration of donor nucleic acid into target nucleic acid. Typically, the second domain is derived from an integrase protein. One preferred integrase protein is a retroviral integrase, which includes HIV-1 (Bushman, pages 6-12; more specifically, see page 6, parag. 1-3 under Detailed Description of the Invention, page 9, 3rd parag., page 10, 3rd parag. to page 11). With regard to the claims being drawn to specifically named endonucleases (claims 16-18), Mannino et al. and Dujon et al. teach that these endonucleases were

known and that in line with the teaching of Bushman, an artisan would have used I-Ppol, Cre1, and H98A because the DNA binding domains of these enzymes bind to very specific regions of DNA because they must bind to a very long stretch of DNA (15-40 base pairs) and would thus have a small number of potential sites to integrate into the genome. It is noted that with regard to Applicant providing an argument only to Bushman, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant indicates that the secondary references do not cure the deficiencies of Bushman. Mannino et al. and Dujon et al. merely disclose particular endonucleases and mention that they are specific to sites that are rarer in a genome. However, just because these endonucleases are more specific does not mean that the skilled artisan would expect that they could be combined with the integrases disclosed in the Bushman publication to accomplish site-specific integration. Bushman does not suggest that different DNA-binding domains should be investigated or that site-specific integration could be achieved (Applicant's response, page 9). In response, this is not persuasive. As discussed above, Bushman provides guidance for making a chimeric protein that can be used to integrate a transgene of interest into a specific site in the genome. The DNA binding site can be obtained from a number of sources, including restriction enzymes (also known as endonucleases). The endonucleases taught by Mannino et al. and Dujon et al. require a higher number of nucleotides in a sequence before they bind

and as such, the sites that fit this requirement is much lower than other restriction enzymes that require a 4, 6, or 8 nucleotide sequence to bind. With regard to reasonable expectation of success to combine the teachings, Bushman provides guidance for using a number of DNA-binding proteins, including restriction enzymes. Because Bushman provides this teaching, this is indicative of reasonable expectation of success.

Applicant indicates that in order to support a prima facie case of obviousness, an artisan must generally find both the suggestion of the claimed invention and a reasonable expectation of success in making that invention, solely in light of the teachings of the prior art and from gene knowledge in the art. In response, this is not persuasive. Bushman provides guidance for making chimeric proteins that can be used to direct integration a transgene of interest into a genome. The DNA-binding domain can be obtained from a number of sources, including restriction enzymes. Mannino et al. and Dujon et al. teach restriction enzymes, particularly ones that bind to large stretches of DNA. Given that Bushman teaches a need to limit the sites into which a transgene integrates, an artisan would have used the DNA-binding domains of enzymes taught by Mannino et al. and Dujon et al. because finding sequences to which they bind (sequences that are 15-40 nucleotides long) is rare.

Thus, the claims remain rejected.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Wednesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Primary Examiner
Art Unit 1632